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# Case of Granulocyte Colony-Stimulating Factor–Induced Sweet's Syndrome

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**A 33-year-old male was referred with a two-week history of fevers to 40°C and painful, erythematous skin and oral mucosal eruptions that had failed to respond to multiple anti-infectious agents. He had a recent diagnosis of a "myeloproliferative disorder with myelodysplastic features" on bone marrow biopsy, with associated pancytopenia. Two weeks before admission, he had been treated with a course of granulocyte colony-stimulating factor (G-CSF) at a dose of 300 µg/day in an attempt to improve his neutropenia. After four days of treatment, the fever and lesions developed. Infectious evaluation was negative; however, biopsies of the skin and oral mucosal lesions revealed histology consistent with Sweet's syndrome. Intravenous methylprednisolone (30 mg/day) was started with prompt defervescence and resolution of the lesions within days. With the increasing use of G-CSF, Sweet's syndrome is becoming more commonly recognized as an adverse effect. This is the first case of G-CSF–induced Sweet's syndrome to demonstrate gingival involvement. Am. J. Hematol. 61:126–129, 1999.** 

**Key words: G-CSF; Sweet's syndrome; leukopenia**

## INTRODUCTION

Sweet's syndrome was first described as an acute febrile neutrophilic dermatosis by Robert Sweet in 1964 [1]. A system of diagnostic criteria was proposed in 1986 consisting of two major criteria and four minor criteria, with definitive diagnosis based on the presence of both major and at least two minor criteria [2]. In 1989, increased erythrocyte sedimentation rate was added as a fifth minor criterion [3]. The exact etiology of Sweet's syndrome has remained unclear. Proposed theories include direct mechanical or chemical irritation, infectious agent, hypersensitivity reaction, or dysfunctional neutrophilic chemotaxis and phagocytosis [4]. More recent observations have led to the idea that particular cytokines (i.e., granulocyte colony-stimulating factor [G-CSF] and interleukin 6 [IL-6]) are primarily involved in the pathogenesis of the disease [4]. This theory has arisen from studies that have demonstrated elevation of serum G-CSF and IL-6 in comparison with other cytokines during acute exacerbations of Sweet's syndrome [4,5]. The validity of this theory has been substantiated by several recently reported cases of exogenous G-CSF–induced Sweet's syndrome [6–13]. Herein is presented a classic case of G-CSF induced Sweet's syndrome in a neutropenic adult patient.

## CASE REPORT

A 33-year-old man was referred with a diagnosis of "myeloproliferative disorder with dysplastic features" determined by bone marrow biopsy demonstrating 100% cellularity with dysplastic features of myeloid and erythroid precursors. The patient's initial presentation had been pancytopenia. With the above diagnosis (myeloproliferative disorder), he was treated with vincristine (2 mg,

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A

B

C

**Fig. 1. (A) Sweet's lesion at venipuncture site in antecubital fossa on initial presentation; (B) Sweet's lesion at right lateral oral commissure on initial presentation; and (C) Sweet's lesion on gingiva on initial presentation.**

once per week for 4 weeks), prednisone (60 mg/day), and fluoxymesterone (20 mg/day) for 4 weeks. Throughout this time the patient was transfusion dependent for platelets and red cells. After the 4 weeks of therapy, the patient developed neutropenia and was started on G-CSF. Within days, he developed high fevers (up to 40°C) accompanied by painful, erythematous skin and oral mucosal eruptions. At the time of transfer, he had been taking G-CSF (300 μg/day) for 2 weeks. Before G-CSF administration, he had no signs of skin or oral lesions or fever. However, after 4 days of G-CSF, the lesions and fever began. As a result of these symptoms, he was hospitalized and blood and tissue cultures were obtained. Blood cultures showed no organisms and tissue culture (skin biopsy) grew *Staphylococcus simulans.* Despite multiple antibiotics, the fevers persisted and additional skin lesions developed, particularly at sites of minor trauma (Fig. 1A). With worsening fevers and skin lesions despite comprehensive anti-infectious coverage, he was transferred to our institution for management. Examination revealed an ill-appearing male with temperature of 40.1°C. Laboratory studies revealed white blood cell count of $2.0 \times 10^3$/L, absolute neutrophil count of 500, hemoglobin of 8.8 g/dl, platelet count of 21,000/L, and erythrocyte sedimentation rate (ESR) of 112 mm/hr. Skin examination was significant for warm, tender, violaceous, hemorrhagic vesicles and nodules with central necrosis and purulence measuring 1 to 4 cm in diameter located on the medial thighs, dorsum of left hand, right antecubital fossa at a venipuncture site, and right lateral oral commissure (Fig. 1A,B). Extensive hemorrhagic

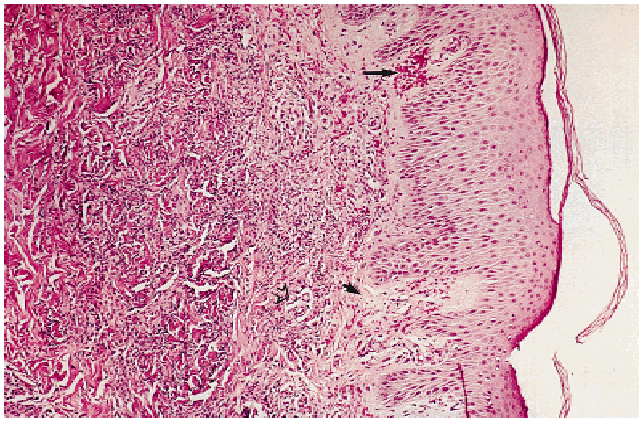

**Fig. 2. Sweet's lesion biopsy specimen shows a dense superficial neutrophilic infiltrate with marked papillary dermal edema (short arrow), foci of dermal hemorrhage (long arrow), and vascular inflammation without vasculitis (open arrow).**

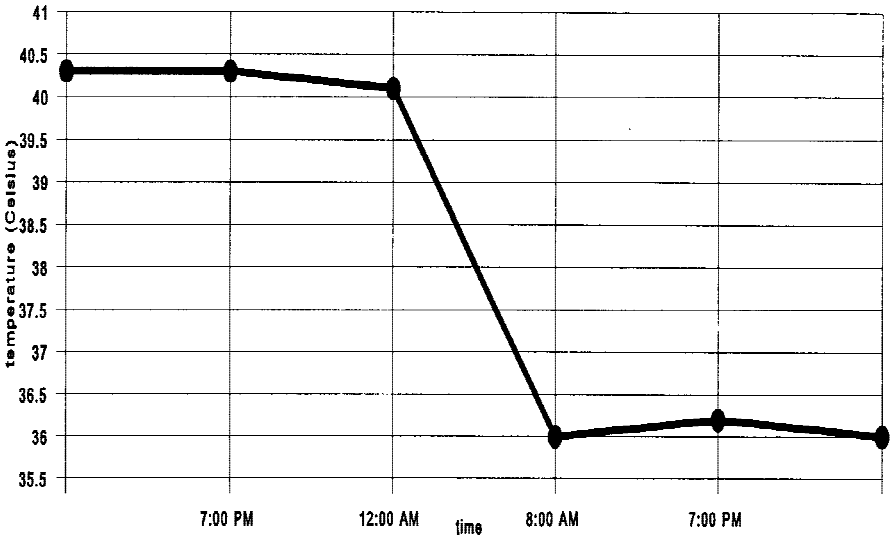


**Fig. 3. Temperature curve, arrow indicates time of initiation of steroid therapy.**

A

B

C

**Fig. 4. (A) Resolving antecubital lesion four days after initiation of therapy; (B) resolving oral commissure lesion four days after initiation of therapy; and (C) resolving gingival lesion four days after initiation of therapy.**

bullae were also found on the labial mucosa and gingiva (Fig. 1C). Biopsy of the skin and oral lesions revealed neutrophilic infiltration consistent with Sweet's syndrome. The lesions (Fig. 2) revealed a dense superficial neutrophilic infiltrate with marked papillary dermal edema, foci of dermal hemorrhage, and vascular inflammation without vasculitis. Tissue culture and special stains for microorganisms including bacteria, fungi, acid fast, mycobacteria, and herpes simplex virus were negative.

Following the findings consistent with Sweet's syndrome and a negative infectious evaluation, intravenous methylprednisolone was initiated at a dose of 30 mg/day. There was a prompt clinical response after the first dose,

with rapid defervescence (Fig. 3). After four days of methylprednisolone, the skin and oral mucosa lesions were significantly improved (Fig. 4), the ESR was decreased to 50 mm/hr, and the temperature remained normal. G-CSF was never restarted and the methylprednisolone was tapered over one month, at which time there were no residual signs or symptoms of Sweet's syndrome.

## DISCUSSION

This case is a clear illustration of G-CSF–induced Sweet's syndrome as demonstrated by the classic febrile pattern, skin lesions, biopsy findings, and laboratory studies that fit the proposed diagnostic criteria [2]. Additionally, skin lesions developed at sites of trauma (i.e., venipuncture), a common characteristic of Sweet's syndrome referred to as pathergy or Koebner's phenomenon [13]. Sweet's syndrome is well-described in association with infections, hematopoietic disorders, solid tumors, paraproteinemias, inflammatory bowel disease, rheumatologic disease, drug associations, and other systemic disorders [14]. In one review, myelodysplastic syndromes, acute nonlymphocytic leukemia, and myeloproliferative disorders were commonly associated [14]. Nevertheless, in the current case, the onset of Sweet's syndrome was clearly related to the use of exogenous G-CSF given the close temporal relationship of symptoms with the institution of therapy. In addition, there was immediate resolution of symptoms with termination of G-CSF therapy and administration of corticosteroid treatment. Exogenous G-CSF–induced Sweet's syndrome is becoming an increasingly recognized phenomenon as demonstrated by recently reported cases in which there is a consistent onset of symptoms within 1 to 2 weeks of G-CSF initiation, regardless of the underlying malignancy [15]. Of particular significance, ours is the first case reported in which G-CSF–induced Sweet's syndrome produced gingival lesions.

These cases have important implications in that they help to support a theory for the pathogenesis of Sweet's syndrome. It has been theorized that endogenous G-CSF may play a significant role in Sweet's syndrome by stimulating the production, activation, maturation, and chemotaxis of neutrophils [8]. In cases of Sweet's syndrome without exogenous G-CSF, it has been demonstrated that shortly before the onset of symptoms, the G-CSF serum level increases dramatically, and then slowly declines during the recovery phase [4]. The rise in G-CSF is believed to lead to an increase in peripheral neutrophils and neutrophilic infiltration of the dermis [4,5]. Therefore, G-CSF may play a critical role in the pathogenesis of Sweet's syndrome, even in patients not receiving exogenous G-CSF.

In conclusion, it is imperative to the patient's welfare to recognize Sweet's syndrome as a true adverse consequence of G-CSF therapy. Patients receiving G-CSF usually have a debilitating disease and Sweet's syndrome adds to the suffering by producing high fevers and painful skin lesions that can often confuse the overall clinical picture. It is important to weigh the risks and benefits of G-CSF therapy as well as recognize and treat the adverse consequences when they occur. With increasing acceptance of G-CSF for a wide variety of neutropenic conditions, physicians must keep these consequences in mind to serve the overall best interest of the patient.

## REFERENCES


1. Sweet RD. An acute febrile neutrophilic dermatosis. Br J Dermatol 1964;76:349–356.
2. Su WPD, Liu H-NH. Diagnostic criteria for Sweet's syndrome. Cutis 1986;37:167–174.
3. von den Driesch P, Gomez RS, Kiesewetter F, and Hornstein OP: Sweet's syndrome: clinical spectrum and associated conditions. Cutis 1989;44:193–200.
4. Reuss-Borst MA, Muller CA, Waller HD. The possible role of G-CSF in the pathogenesis of Sweet's syndrome. Leuk Lymphoma 1994;15: 261–264.
5. Reuss-Borst MA, Pawelec G, Saal JG, Horny HP, Muller CA, Waller HD. Sweet's syndrome associated with myelodysplasia: possible role of cytokines in the pathogenesis of the disease. Br J Haematol 1993; 84:356–358.
6. Jain KK. Sweet's syndrome associated with granulocyte colony-stimulating factor. Cutis 1996;57:107–110.
7. Paydas S, Sahin B, Seyrek E, Soylu M, Gonlusen G, Acar A, Tuncer I. Sweet's syndrome associated with G-CSF. Br J Dermatol 1993;85: 191–192.
8. Fukutoku M, Shimizu S, Ogawa Y, Takeshita S, Masaki Y, Arai T, Hirose Y, Sugai S, Konda S, Takiguchi T. Sweet's syndrome during therapy with granulocyte colony-stimulating factor in a patient with aplastic anemia. Br J Haematol 1994;86:645–648.
9. Prevost-Blank PL, Shwayder TA. Sweet's syndrome secondary to granulocyte colony-stimulating factor. J Am Acad Dermatol 1996;35: 995–997.
10. Shimizu T, Yoshida I, Eguchi H, Takahashi K, Inada H, Ando A, Kato H. Sweet syndrome in a child with aplastic anemia receiving recombinant granulocyte colony-stimulating factor. J Pediatr Hematol Oncol 1996;18:282–284.
11. Richard MA, Grob JJ, Laurans R, Hesse S, Brunet P, Stoppa AM, Bonerandi JJ, Berland Y, Maraninchi D. Sweets syndrome induced by granulocyte colony stimulating factor in a woman with congenital neutropenic. J Am Acad Dermatol 1996;35:629–631.
12. Park JW, Mehrotra B, Barnett BO, Baron AD, Venook AP. The Sweet syndrome during therapy with granulocyte colony-stimulating factor. Ann Intern Med 1992;116:996–998.
13. Van Kamp H, Van Den Berg E, Timens W, Kraaijenbrink RA, Halie MR, Daenen SMGJ. Sweet's syndrome in myeloid malignancy: a report of two cases. Br J Haematol 1994;86:415–417.
14. Fett DL, Gibson LE, Su WPD. Sweet's syndrome: systemic signs and symptoms and associated disorders. Mayo Clin Proc 1995;70:234–240.
15. Johnson MML, Grimwood RE. Leukocyte colony-stimulating factors. Arch Dermatol 1994;130:77–81.